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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,976	05/10/2001	Tse W. Chang	THI-001	4934

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,976	CHANG ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,14-16,20,26,27,61 and 62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,14-16,20,26,27,61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/29/04 has been entered.

2. Claims 3, 14-16, 20, 26-27, 61 and 62 are pending.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3, 14-16, 20, 26-27, 61 and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an immunogenic composition comprising a pharmaceutically acceptable carrier and a first human polypeptide coupled to or fused to a second non-human polypeptide, wherein the first polypeptide consisting of the extracellular domain of a polypeptide specifically expressed on the surface of activated B cells selected from the group consisting of CD79α, CD79β and CD20 or immunogenic portion thereof and wherein the second polypeptide is an Fc fragment of a non-human immunoglobulin molecule that contains a T cell epitope, the composition being capable of eliciting an antibody immune response against B cells in a human subject or the composition is capable of reducing or eliminating the population of cells expressing the first polypeptide wherein the fusion protein is dimeric, **does not** reasonably provide enablement for all first polypeptide "comprises" any "immunogenic portion" (claims 3 and 20) of a first polypeptide such as CD79α, CD79β and CD20 expressed on the surface of activated B cells coupled to or fused to (claims 14, and 26) a second non-human polypeptide wherein the second polypeptide is an Fc fragment of a non-human immunoglobulin that contains at least one T helper cell epitope in the claimed composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only an immunogenic composition comprising a pharmaceutically acceptable carrier and a first human polypeptide coupled to a second non-human polypeptide, wherein the first polypeptide *consisting* of the *extracellular domain* of a polypeptide specifically expressed on the surface of activated B cells selected from the group consisting of CD79α, CD79β and CD20 or immunogenic portion thereof and wherein the second polypeptide is an Fc fragment of a non-human immunoglobulin molecule that contains a T cell epitope, the composition being capable of eliciting an antibody immune response against B cells in a human subject (claim 3) or the composition is capable of reducing or eliminating the population of cells expressing the first polypeptide (claim 20).

The specification does not teach how to make all first polypeptide comprising any *immunogenic portion* of CD79α, CD79β and CD20 that expressed on activated B cells because the term "comprising" is open-ended. It expands the immunogenic portion to include additional amino acids at either or both ends. There is insufficient guidance as to which amino acids to be added and whether the resulting first polypeptide coupled to a second non-human polypeptide would induce antibody immune response that is specific for the CD79α, CD79β and CD20 on the surface of activated B cells in a human subject.

Kuby *et al*, of record, teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Further, there is insufficient in vivo working examples demonstrating that all first polypeptide comprises extra amino acids and immunogenic portion of CD79α, CD79β or CD20 either fused to or coupled to an Fc fragment of non-human immunoglobulin molecule that contains at least one T helper cell epitope (second polypeptide) in the claimed composition are capable of eliciting antibody immune response against B cells in a human subject.

Without the amino acid sequence, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

5. Claims 3, 14-16, 20, 26-27, 61 and 62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* first polypeptide "comprises" any "immunogenic portion" of a first polypeptide such as CD79α, CD79β and CD20 expressed on the surface of activated B cells coupled to a second non-human polypeptide wherein the second polypeptide is an Fc fragment of a non-human immunoglobulin that *contains at least one T helper cell epitope* in the claimed composition as set forth in claims 3 and 20).

The specification discloses only an immunogenic composition comprising a pharmaceutically acceptable carrier and a first human polypeptide coupled to a second non-human polypeptide, wherein the first polypeptide consisting of the extracellular domain of a polypeptide specifically expressed on the surface of activated B cells selected from the group consisting of CD79α, CD79β and CD20 or immunogenic portion thereof and wherein the second polypeptide is an Fc fragment of a non-human immunoglobulin molecule that contains a T cell epitope, the composition being capable of eliciting an antibody immune response against B cells

in a human subject (claim 3) or the composition is capable of reducing or eliminating the population of cells expressing the first polypeptide (claim 20).

With the exception of the specific immunogenic composition mentioned above, there is inadequate written description about the "immunogenic portion" of the first polypeptide in the claimed composition because the term "comprising" is open-ended. It expands the immunogenic portion of the first polypeptide to include additional amino acids at either or both ends. There is insufficient written description about which amino acids to be added and whether the resulting first polypeptide coupled to a second non-human polypeptide would induce antibody immune response that is specific for the CD79α, CD79β and CD20 on the surface of activated B cells in a human subject. Since the antibody is not specific, it follows that the composition is capable of reducing or eliminating the population of cells expressing the first polypeptide is not adequately described.

The specification discloses only the first polypeptide consisting of the extracellular domain of mouse CD79α, CD79β and CD20 fused to the second polypeptide wherein the second polypeptide is human Fc domain, the second polypeptide is an Fc fragment of a non-human immunoglobulin that contains at least one T helper T cell epitope in the claimed composition is not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claim 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "concentration of cells expressing the polypeptide" in claim 62, line 2 is ambiguous and indefinite because it is not clear which polypeptide is being expressed on the cell surface.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 3, 14-15, 20, 26-27 and 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al (J of Allergy and Clinical Immunology 105(1) part 2: S106, Jan 2000; PTO 1449) in view of Tedder et al (J Immunol 142(7): 2560-8, April 1989; PTO 892), and McLaughlin et al (J Clin Oncol 16(8): 2825-33, Aug 1998; PTO 892) and Zambidis *et al* (Proc Natl Acad Sci USA 93: 5019-5024, May 1996; PTO 892) as evident by Isaacs *et al* (of record, British J of Rheumatology 36: 305-309, 1997; PTO 892).

Huang *et al* teach a pharmaceutical composition comprising a fusion protein comprising a first self CD20 peptide such as the extracellular segment of 46 amino acids of mouse CD20 from mouse that specifically expressed on the surface of activated B cells linked to or fused a foreign polypeptide such as CH2-CH3 domains of human gamma 1 immunoglobulin (See S106 abstract, in particular). The reference composition is capable of eliciting an antibody immune response to self CD20 in the subject such as mouse. The reference foreign Fc fragment contains T helper cell epitope (See abstract, 3rd paragraph, in particular). The reference composition is effective for reducing antibody response to self CD20 and is capable of eliminating the population of B cells in the subject expressing the CD20 polypeptide (See abstract, 4th paragraph, in particular). The reference fusion protein is dimeric because of disulfide bond that forms in Fc region. Huang *et al* specific autoimmune anti-CD20 antibodies can be induced against self CD20 coupled to a foreign

peptide and CD20 antigen is an attractive target for immunological intervention for the purpose of regulating B cell activity and eliminating B-cell lymphoma (See abstract, 1st and last paragraph, in particular).

The claimed invention as recited in claims 3, and 20 differs from the teachings of the references only in that the first polypeptide comprises a human CD20 fused to any IgG Fc instead of mouse CD20 fused to human IgG Fc.

Tedder *et al* teach human CD20 is a differentiation antigen found only on the surface of B cells and regulates human B cell proliferation and differentiation (See abstract, in particular).

McLaughlin *et al* teach human CD20 is expressed on more than 90% of B cell lymphomas and CD20 is appealing for targeted therapy because it does not shed or modulate (See abstract, in particular).

Zambidis *et al* teach heterologous immunoglobulins have been shown to be extremely effective as tolerogenic carriers for nearly 30 years and the efficacy of these proteins is due in part to their long half-life in vivo as well as their ability to crosslink surface IgM with Fc receptors (See abstract, in particular). Zambidis et al teach fusion protein of mouse IgG1 with the immunodominant epitope of 12-26 from bacteriophage λ cI repressor protein which contains T cell epitope enhances immune response to the heterologous oligopeptide (See abstract, page 5029, col. 2, in particular).

Isaacs *et al* teach various fusion proteins such as extracellular domain of CD4 molecule fused to the part of immunoglobulin such as the hinge, CH2 and CH3 domains or CTLA4-Ig (see page 305, in particular). Isaacs *et al* teach that the Fc region of the immunoglobulin endows the fusion protein with specific properties such as prolonged the circulating half life, enabled dimerization thereby increasing avidity for the ligand and it provides effector function such as opsonization by Ig for enhanced phagocytosis or complement mediated lysis (See page 305, column 1, in particular). However, Isaacs *et al* teach that because their sequences such as CD4 and Fc are derived from self-proteins, they are less immunogenic (See page 305, second paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to swap the extra cellular domain of mouse CD20 as taught by Huang et al for the extra cellular domain of human CD20 Tedder *et al* or McLaughlin *et al* and substitute the 12-26 from bacteriophage λ cI repressor protein in the fusion protein as taught by Zambidis et al or the CD4 extracellular domain as taught by Isaacs et al for the human CD20 as taught by

Tedder et al and McLanghlin et al for a fusion protein comprising a human CD20 polypeptide coupled to a non-self or heterologous Fc fragment of a mouse Ig1 immunogloublin that contains a T cell helper cell epitope that elicits an antibody response against B cells in a human subject as taught by the Huang et al, Tedder *et al,* Zambidis *et al* and Zambidis *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Huang *et al* specific autoimmune anti-CD20 antibodies can be induced against self CD20 coupled to a foreign peptide and CD20 antigen is an attractive target for immunological intervention for the purpose of regulating B cell activity and eliminating B-cell lymphoma (See abstract, 1st and last paragraph, in particular). Zambidis et al teach fusion protein of mouse IgG1 with the immunodominant epitope of 12-26 from bacteriophage λ cI repressor protein which contains T cell epitope enhances immune response to the heterologous oligopeptide (See abstract, page 5029, col. 2, in particular) and heterologous immunoglobulins have been shown to be extremely effective as tolerogenic carriers for nearly 30 years and the efficacy of these proteins is due in part to their long half-life in vivo. McLaughlin *et al* teach human CD20 is expressed on more than 90% of B cell lymphomas and CD20 is appealing for targeted therapy because it does not shed or modulate (See abstract, in particular). Isaacs *et al* teach that self-proteins such as CD4 and Fc are less immunogenic (See page 305, second paragraph, in particular). Claims 61-62 are included in this rejection because Huang *et al* teach self CD20 peptide such as the extracellular segment of 46 amino acids of mouse CD20 from mouse that specifically expressed on the surface of activated B cells linked to or fused a foreign polypeptide such as CH2-CH3 domains of immunoglobulin is effective for eliminating B-cell lymphoma (See abstract, 1st and last paragraph, in particular) and the inherent properties of the fusion protein cannot be separated from the product.

11. Claims 3, 14-15, 20, 26-27 and 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al (J of Allergy and Clinical Immunology 105(1) part 2: 142.9, Jan 2000; PTO 1449) or Hashimoto *et al* (of record, Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* or Huang et al (J of Allergy and Clinical Immunology 105(1) part 2: 142.10, Jan 2000; PTO 1449) each in view of Zambidis *et al* (Proc Natl Acad Sci USA 93: 5019-5024, May 1996; PTO

892) as evident by Isaacs *et al* (of record, British J of Rheumatology 36: 305-309, 1997; PTO 892).

Huang *et al* teach a pharmaceutical composition comprising a fusion protein comprising a first human CD79α (Igα) coupled to a CH2-CH3 domain of human gamma 1 immunoglobulin (See abstract, in particular). The reference pharmaceutical composition induces autoantibodies against self human CD79α (Igα) and total B cells in immunized mice declined after the elicitation of autoantibodies (See abstract, in particular).

Hashimoto *et al* teach a polypeptide such as human and mouse CD79α (Ig-α/mb-1) that is a B cell-associated antigen that forms heterodimer with CD79β to become a B cell surface receptor (See page 287, column 2, page 288, Figures 1&2, in particular). The reference polypeptide human CD79α (Ig-α/mb-1) forming complex with CD79β is critical for both cell surface expression and signaling functions of the B cell receptor (BCR) (See page 287, column 2, in particular).

Kooten *et al* teach that CD79α (Ig-α/mb-1) and Ig-β (B29 or CD79β) together form the B cell receptor and play a critical role in the development of B cells (See page 509, column 1, first paragraph, in particular). Kooten *et al* teach that that the same receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular).

Huang *et al* teach a pharmaceutical composition comprising a fusion protein comprising a first mouse CD79β (Igβ) coupled to a foreign CH2-CH3 domain of human gamma 4 immunoglobulin (See abstract, in particular). The foreign human gamma 4 component is able to provide antigenic determinants for helper T cells. The reference pharmaceutical composition induces autoantibodies against self CD79β (Igβ) and total B cells in immunized mice declined by about 30% as compared to control mice (See abstract, in particular). Huang *et al* teach specific autoimmune antibodies against self CD79β can be actively induced by immunizing with CD79β coupled to a foreign antigen (See abstract, in particular).

The claimed invention as recited in claims 3, and 20 differs from the teachings of the references only in that the first polypeptide comprises a human CD79α or human CD79β fused to any IgG Fc instead of human IgG Fc.

Zambidis *et al* teach heterologous immunoglobulins have been shown to be extremely effective as tolerogenic carriers for nearly 30 years and the efficacy of these proteins is due in part to their long half-life in vivo as well as their ability to crosslink surface IgM with Fc

receptors (See abstract, in particular). Zambidis et al teach fusion protein of mouse IgG1 with the immunodominant epitope of 12-26 from bacteriophage λ cI repressor protein which contains T cell epitope enhances immune response to the heterologous oligopeptide (See abstract, page 5029, col. 2, in particular).

Isaacs *et al* teach various fusion proteins such as extracellular domain of CD4 molecule fused to the part of immunoglobulin such as the hinge, CH2 and CH3 domains or CTLA4-Ig (see page 305, in particular). Isaacs *et al* teach that the Fc region of the immunoglobulin endows the fusion protein with specific properties such as prolonged the circulating half life, enabled dimerization thereby increasing avidity for the ligand and it provides effector function such as opsonization by Ig for enhanced phagocytosis or complement mediated lysis (See page 305, column 1, in particular). However, Isaacs *et al* teach that because their sequences such as CD4 and Fc are derived from self-proteins, they are less immunogenic (See page 305, second paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the 12-26 from bacteriophage λ cI repressor protein in the fusion protein as taught by Zambidis et al for the human CD79α as taught by Huang et al and Hashimoto *et al*, or the human Ig-β (B29 or CD79β) as taught by Kooten *et al* for a fusion protein comprising a human CD79α or a human CD79β polypeptide coupled to a heterologous Fc fragment of a mouse Ig1 immunogloublin that contains a T cell helper cell epitope that elicits an antibody response against B cells in a human subject as taught by the Huang et al, Zambidis *et al,* Hashimoto *et al*, and Kooten *et al.* Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human CH2-CH3 domains of human gamma 1 immunoglobulin in the fusion protein as taught by Huang et al for the mouse IgG1 that contains T cell epitope to enhance immune response to the heterologous oligopeptide as taught by Zambidis *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Zambidis et al teach fusion protein of mouse IgG1 with the immunodominant epitope of 12-26 from bacteriophage λ cI repressor protein which contains T cell epitope enhances immune response to the heterologous oligopeptide (See abstract, page 5029, col. 2, in particular) and heterologous immunoglobulins have been shown to be extremely effective as tolerogenic carriers

for nearly 30 years and the efficacy of these proteins is due in part to their long half-life in vivo. Huang *et al* teach specific autoimmune antibodies against self CD79α CD79β can be actively induced by immunizing with CD79β coupled to a foreign antigen (See abstract, in particular). Kooten *et al* teach that that the same receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular). Isaacs *et al* teach that self-proteins such as CD4 and Fc are less immunogenic (See page 305, second paragraph, in particular). Claims 61-62 are included in this rejection because the eliminating B-cell is an inherent property of the reference fusion protein and inherent properties of the product cannot be separated from the product.

12. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al (J of Allergy and Clinical Immunology 105(1) part 2: S106, Jan 2000; PTO 1449) in view of Tedder *et al* (J Immunol 142(7): 2560-8, April 1989; PTO 892), and McLaughlin *et al* (J Clin Oncol 16(8): 2825-33, Aug 1998; PTO 892) and Zambidis *et al* (Proc Natl Acad Sci USA 93: 5019-5024, May 1996; PTO 892) as evident by Isaacs *et al* (of record, British J of Rheumatology 36: 305-309, 1997; PTO 892) as applied to claims 3, 14-15, 20, 26-27 and 61-62 and further in view of US 5,116,964 (May 1992; PTO 892).

The combined teachings of Huang *et al*, Tedder *et al,* McLaughlin *et al* and Zambidis *et al* as evident by Isaacs *et al* have been discussed supra.

The claimed invention in claim 16 differs from the combined teachings of the references only in that the immunogenic composition wherein the firs polypeptide and the second polypeptide are coupled via a chemical linkage.

The '964 patent teaches immunoglobulin fusion polypeptide such as CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The '964 patent further teaches the CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof can be chemical crosslink via cross-linking agents such as N-hydroxysuccimide esters that are commonly known to one ordinary skill in the art (See col. 22, lines 1-10, in particular). The advantage of immunoglobulin fusion polypeptide extends the half-lives of the fusion protein or conjugate and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to crosslink the first polypeptide such as self human CD20 polypeptide as taught by Tedder et al and McLanghlin et al to the heterologous polypeptide such as the Fc fragment of a mouse Ig1 immunogloublin that contains a T cell helper cell epitope as taught by Zambidis *et al* to elicit an antibody response against human B cells in a human subject as taught by the Huang et al, and extend the half life of the conjugate as taught by the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '964 patent teaches that the advantage of immunoglobulin chemically coupled polypeptide extends the half-lives of the polypeptide or conjugate and is useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular). Further, chemical linkage is commonly known to one of ordinary skill in the art. Huang *et al* specific autoimmune anti-CD20 antibodies can be induced against self CD20 coupled to a foreign peptide and CD20 antigen is an attractive target for immunological intervention for the purpose of regulating B cell activity and eliminating B-cell lymphoma (See abstract, 1st and last paragraph, in particular). Zambidis et al teach fusion protein of mouse IgG1 with the immunodominant epitope of 12-26 from bacteriophage λ cI repressor protein which contains T cell epitope enhances immune response to the heterologous oligopeptide (See abstract, page 5029, col. 2, in particular) and heterologous immunoglobulins have been shown to be extremely effective as tolerogenic carriers for nearly 30 years and the efficacy of these proteins is due in part to their long half-life in vivo. McLaughlin *et al* teach human CD20 is expressed on more than 90% of B cell lymphomas and CD20 is appealing for targeted therapy because it does not shed or modulate (See abstract, in particular). Isaacs *et al* teach that self-proteins such as CD4 and Fc are less immunogenic (See page 305, second paragraph, in particular).

13. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al* (J of Allergy and Clinical Immunology 105(1) part 2: 142.9, Jan 2000; PTO 1449) or Hashimoto *et al* (of record, Immunogenetics 40: 287-295, 1994; PTO 892) or Kooten *et al* or Huang *et al* (J of Allergy and Clinical Immunology 105(1) part 2: 142.10, Jan 2000; PTO 1449) each in view of Zambidis *et al* (Proc Natl Acad Sci USA 93: 5019-5024, May 1996; PTO 892) as evident by

Isaacs *et al* (of record, British J of Rheumatology 36: 305-309, 1997; PTO 892) as applied to claims 3, 14-15, 20, 26-27 and 61-62 and further in view of US 5,116,964 (May 1992; PTO 892).

The combined teachings of Huang *et al*, Hashimoto *et al*, Kooten *et al*, Huang *et al* Zambidis *et al* as evident *by* Isaacs *et al* have been discussed supra.

The claimed invention in claim 16 differs from the combined teachings of the references only in that the immunogenic composition wherein the firs polypeptide and the second polypeptide are coupled via a chemical linkage.

The '964 patent teaches immunoglobulin fusion polypeptide such as CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The '964 patent further teaches the CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof can be chemical crosslink via cross-linking agents such as N-hydroxysuccimide esters that are commonly known to one ordinary skill in the art (See col. 22, lines 1-10, in particular). The advantage of immunoglobulin fusion polypeptide extends the half-lives of the fusion protein or conjugate and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to crosslink the first polypeptide such as self human CD79α as taught by Huang et al and Hashimoto *et al*, or the human Ig-β (B29 or CD79β) as taught by Kooten *et al* to the heterologous Fc fragment of a mouse Ig1 immunogloublin that contains a T cell helper cell epitope as taught by Zambidis *et al* to elicit an antibody response against human B cells in a human subject as taught by the Huang et al, Zambidis *et al,* Hashimoto *et al*, and Kooten *et al* and extends the half life of the conjugate as taught by the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '964 patent teaches the advantage of immunoglobulin chemically coupled polypeptide extends the half-lives of the polypeptide or conjugate and is useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular). Further, chemical linkage is commonly known to one of ordinary skill in the art. Zambidis et al teach fusion protein of mouse IgG1 with the immunodominant epitope of 12-26 from bacteriophage λ cI repressor protein which contains T cell epitope enhances immune response to the heterologous oligopeptide (See abstract, page 5029,

col. 2, in particular) and heterologous immunoglobulins have been shown to be extremely effective as tolerogenic carriers for nearly 30 years and the efficacy of these proteins is due in part to their long half-life in vivo. Huang *et al* teach specific autoimmune antibodies against self CD79α CD79β can be actively induced by immunizing with CD79β coupled to a foreign antigen (See abstract, in particular). Kooten *et al* teach that that the same receptor can be used for negative selection processes to eliminate B cells with specificity for autoantigens (See page 510, column 1, first paragraph, in particular). Isaacs *et al* teach that self-proteins such as CD4 and Fc are less immunogenic (See page 305, second paragraph, in particular).

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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